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Differential Metabolic Effects of Beta-Blockers: an Updated Systematic Review of Nebivolol

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Abstract Blood pressure management in hypertensive patients with metabolic abnormalities is challenging, since many of the antihypertensive drugs adversely affect metabolism. Besides effective control of blood pressure in patients with hypertension, third-generation beta-blockers such as nebivolol offer additional benefits for central hemodynamics and neutral or beneficial effects on metabolism. Emerging clinical data suggest that nebivolol also has similar effects on metabolism in obese hypertensive and hypertensive diabetic patients. The present article will provide a systematic analysis of the pathophysiological links among hypertension, insulin resistance, and metabolic syndrome. We will also summarize the available clinical evidence regarding the metabolic effects of beta-blockers in hypertensive patients, with an emphasis on nebivolol. Nebivolol exerts neutral or beneficial effects on insulin sensitivity and lipid metabolism in hypertensive patients, owing to its nitric oxide-mediated vasodilatory and antioxidative properties. Thus, nebivolol could be a favorable therapeutic option for the treatment of hypertension in patients with impaired glucose and lipid metabolism.

Keywords Hypertension · Insulin sensitivity · Lipid metabolism · Nebivolol · Obesity

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Introduction

A high prevalence of metabolic abnormalities is observed in hypertensive patients. In particular, these patients have a 2.5-fold higher risk of developing type 2 diabetes when compared to normotensives [1]. In addition, approximately 70% of hypertensive patients are overweight. Along with other metabolic cardiovascular risk factors, such as insulin resistance and dyslipidemia, hypertension is also included among the criteria for metabolic syndrome [2].

Over the last few years, many classes of antihypertensive drugs have been used to control blood pressure in hypertensive patients. The metabolic effects of these antihypertensive agents should be considered with a view to improving the long-term prognosis. The adverse metabolic effects of some antihypertensive drugs, such as conventional beta-blockers, may offset their beneficial blood pressure (BP)-lowering effects. Hence, the chosen antihypertensive treatment should offer benefits beyond BP control while avoiding adverse effects that could have a prognostic impact.

Nebivolol is a third-generation beta-blocker [3]. It is a racemic mixture of a D- and an L-isomer (1:1), of which d-nebivolol displays antagonistic activity that is highly selective for the beta-1 adrenergic receptor. The affinity of d-nebivolol for beta-1 adrenoceptors is approximately 175 times greater than that of l-nebivolol [4]. The L-isomer of nebivolol causes the stimulation of endothelial nitric oxide synthase (eNOS) and subsequent endothelium-dependent vasodilation. Nebivolol has a unique profile among antihypertensive drugs: high selectivity for the beta-1 adrenergic receptor, agonistic action on beta-3 receptors, and nitric oxide (NO)-mediated vasodilatory and antioxidant properties. NO is an important bioactive signaling molecule that mediates a variety of normal physiological functions and may regulate glucose metabolism through multiple pathophysiologic mechanisms (Table 1).

Table 1 Possible mechanisms of nitric oxide metabolic effects

- Anti-inflammatory and antioxidant properties
- Regulation of mitochondrial respiration and mitochondrial biogenesis
- Regulation of the binding and release of oxygen with hemoglobin
- Activation of peroxisome proliferator-activated gamma receptors
- Smooth muscle relaxation and vasodilation
- Increase of blood flow at sites of very low oxygen concentrations

Owing to the combination of these properties, nebivolol is associated with clinically significant improvement in BP control in hypertensive patients. It is well tolerated and appears to exert far fewer adverse metabolic effects when compared to other beta blockers [5–8, 9••, 10].

In this review article, we will discuss the pathophysiological links between hypertension and other metabolic conditions in patients with insulin resistance, obesity, dyslipidemia, and metabolic syndrome. We will summarize the clinical evidence concerning the metabolic effects of the commonly used beta-blockers in hypertensive patients. We will also provide a critical review of the available clinical trial data regarding the effects of the new-generation beta-blockers in hypertensive patients, emphasizing the impact of nebivolol on insulin resistance and dyslipidemia and its implications for comprehensive clinical management.

Insulin Sensitivity and Glucose Metabolism in Hypertensive Patients

Insulin is an important hormone that plays a crucial role in the regulation of glucose, lipid metabolism, and energy storage. It is an anabolic hormone with complex vascular actions that might be beneficial or deleterious to the arterial wall [11]. The protective effects, such as vasodilation, are mediated by NO-dependent mechanisms in the endothelium, while the deleterious effects of insulin, such as vasoconstriction, proliferation of vascular smooth muscle cells, and proinflammatory activity, are mediated through the mitogen-activated protein kinase (MAPK) pathway [11]. In clinical conditions with insulin resistance, the insulin-stimulated NO pathway is selectively impaired and the MAPK pathway is overactivated [12, 13]. This results in an increase in proinflammatory mediators, sodium and water retention, vasoconstriction, and finally, elevation of BP. Insulin-mediated glucose uptake is linked with NO-dependent vasodilation, since they share similar signaling pathways [14].

Hypertension is often associated with impaired glucose metabolism and insulin sensitivity. There is a plethora of published data relating hypertension and insulin resistance, a combination that often leads to an increased risk of diabetes type 2 and cardiovascular disease. Angiotensin, which may be overactivated in hypertension, contributes to β-cell dysfunction and has a detrimental effect on insulin secretion [15].

Clinical studies have shown that approximately 50% of individuals with elevated BP also have insulin resistance. Although the association between insulinemia and hypertension is controversial, there is evidence of a possible link between insulin, hypertension, and type 2 diabetes [7]. Insulin resistance may also lead to prediabetes and diabetes [16].

Insulin resistance increases pancreatic beta-cell activity; this leads to hyperinsulinemia, which causes impaired glucose tolerance, hyperglycemia, and overt diabetes. An association between hyperinsulinemia and hypertension has been reported in both obese and nonobese individuals [17]. Insulin activates the sympathetic nervous system (SNS), increases renal tubular sodium reabsorption, alters ion transport, enhances sodium reabsorption by the kidney, and causes hypertrophy of vascular smooth muscle [18]. SNS activation appears to be the common pathophysiological pathway linking insulin resistance and hypertension. In physiological conditions, insulin stimulates NO production and vasorelaxation. In contrast, in insulin-resistant conditions, the insulin-stimulated NO pathway is impaired and compensatory hyperinsulinemia may activate inflammation and vasoconstriction. Diabetes and hypertension share common pathways, such as overactivation of the SNS, the renin–angiotensin–aldosterone system (RAAS), oxidative stress, and adipokines, which play a fundamental role in vascular pathophysiology [19]. Diabetes and hypertension also share common pathways, such as the SNS, RAAS, oxidative stress, adipokines, insulin resistance, and peroxisome proliferator-activated receptors, which interact and influence each other.

Different classes of antihypertensive drugs exert differential effects on metabolic status and glucose homeostasis [1]. Calcium-channel blockers do not adversely affect glucose metabolism, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACE-i) improve glucose metabolism, whereas conventional nonvasodilatory beta-blockers and diuretics are associated with impaired glucose metabolism.

Hypertension in Patients with Metabolic Syndrome

Metabolic syndrome is a cluster of metabolic risk factors that include abdominal obesity, dyslipidemia, elevated plasma glucose, hypertension, and insulin resistance. The definition of metabolic syndrome by the Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) is widely accepted [20]. According to these guidelines, metabolic syndrome can be defined as a condition in which 3 or more of the following risk factors are present: BP ≥130/85 mmHg (or drug treatment for hypertension), high-density lipoprotein cholesterol (HDL) <1.0 mmol/L (40 mg/dL) in men or <1.3 mmol/L (50 mg/dL)

in women (or drug treatment for reduced HDL), fasting glucose ≥5.6 mmol/L (100 mg/dL) (or drug treatment for elevated glucose), triglycerides >1.7 mmol/L (150 mg/dL) (or drug treatment for elevated triglycerides), and waist circumference >102 cm in men or >88 cm in women. Patients with metabolic syndrome show a high incidence of developing type 2 diabetes mellitus (DM) and cardiovascular complications [21, 22]. Metabolic syndrome raises the risk of incident type 2 DM by approximately 5-fold [22].

Hypertension is strongly associated with the risk of cardiovascular disease in patients with metabolic syndrome. The Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) population study showed the presence of elevated BP in 95.4% of individuals with metabolic syndrome ($n = 2013$) [23]. In the PIUMA study, a total of 1742 Caucasian adult patients with essential hypertension and without cardiovascular diseases (55% men; BP 154/95 mm Hg; age 50 ± 12 years) were followed for up to 10.5 years [24]. Hypertensive patients with metabolic syndrome showed an increased risk of developing cardiovascular and cerebrovascular events, independently of several classic cardiovascular risk factors such as left ventricular hypertrophy and 24-h ambulatory BP parameters [24].

Cardiovascular risk is increased when the risk factors are clustered in metabolic syndrome, as compared to the risk associated with any of its individual components. In a systematic review and meta-analysis study including 951,083 patients, metabolic syndrome was associated with an increased risk of cardiovascular disease (relative risk [RR] 2.35; 95% confidence interval [CI] 2.02 to 2.73), increased cardiovascular mortality (RR 2.40; 95% CI 1.87 to 3.08), and a 1.5-fold increase in all-cause mortality (RR 1.58; 95% CI 1.39 to 1.78) [25]. Individuals with metabolic syndrome displayed an increased risk of myocardial infarction (RR 1.99; 95% CI 1.61 to 2.46) and stroke (RR 2.27; 95% CI 1.80 to 2.85) [25]. In another prospective cohort study including 1209 Finnish men without baseline cardiovascular disease, cancer, or diabetes, followed up for approximately 11.4 years [26], it was observed that, even in the absence of baseline cardiovascular disease and diabetes, the incidence of cardiovascular disease and all-cause mortality was increased in men with metabolic syndrome [25].

Visceral obesity and insulin resistance have been recognized as the main factors involved in the pathophysiology of metabolic syndrome. Visceral obesity is associated with the development of hyperglycemia, hyperlipidemia, and hypertension. Visceral fat represents a metabolically active organ and is strongly related to insulin sensitivity. It moderates the secretion of various adipocytokines, such as leptin and adiponectin, tumor necrosis factor-α, interleukin-6 (IL-6), and nonesterified fatty acids, which in turn induce the development of hypertension [27]. Furthermore, insulin activates the SNS and increases renal sodium reabsorption. This salt-retaining effect of insulin is preserved or may be increased in individuals with insulin resistance, which may lead to the development of hypertension [28]. Oxidative stress is also associated with increased cardiovascular risk in patients with metabolic syndrome. The frequent occurrence of BP abnormalities in the high normal/hypertensive patients with metabolic syndrome is associated with hypertension-related subclinical organ damage, such as left ventricular hypertrophy, arterial stiffening, and increased urinary protein excretion [21, 23, 24]. However, organ damage was also reported in patients who had metabolic syndrome without elevated BP, suggesting that other components of metabolic syndrome may play a role in organ damage that is independent of BP [29].

Effects of Beta-Blockers on Insulin Sensitivity and Glucose Metabolism

A large number of studies in the literature have investigated the metabolic side effects of b-blockers. A substantial amount of data indicated that, because of a deterioration in insulin resistance, vasoconstricting beta-blockers lead to an increased risk of new-onset diabetes and a worsening of glycemic control. A large meta-analysis of 143,153 hypertensive patients revealed that the risk of new-onset diabetes was more pronounced with b-blockers and diuretics and that this was associated with adverse cardiovascular outcomes in the long term [30]. The risk is higher in patients with higher BMI and higher fasting blood glucose levels. However, older studies and meta-analyses were based on older generation b-blockers that have no vasodilatory effect. Conventional beta-blockers such as atenolol, propranolol, and metoprolol negatively affect insulin sensitivity and glucose metabolism and have been found to increase the risk of type 2 diabetes. The International Verapamil–Trandolapril Study (INVEST), which evaluated 22,576 patients with hypertension and coronary artery disease, demonstrated that long-term therapy with atenolol was associated with a 15% higher risk of new-onset diabetes compared with verapamil [31]. Higher plasma atenolol exposure may be a risk factor for an increase in fasting plasma glucose level during atenolol treatment [32].

Several mechanisms have been proposed to elucidate the mechanisms underlying the metabolic effects of conventional beta-blockers. Beta-blockers have effects on metabolism, mainly via their mechanism as blockers of adrenergic stimulation. Treatment with conventional beta-blockers leads to unopposed alpha-1 activity, causing vasoconstriction and decreased blood flow to skeletal muscles, which are an important organ in the regulation of glucose homeostasis. This results in a decrease in insulin-stimulated glucose uptake in muscles, leading to insulin resistance. Insulin secretion from pancreatic beta-cells is also affected by treatment with nonvasodilatory

beta-blockers [33]. By impairing beta2-mediated insulin release, beta-blockers decrease the first phase of insulin secretion and contribute to the development of type 2 diabetes. Another adverse effect of beta-blockers is weight gain, which might be attributable to decreased insulin sensitivity and deterioration of glucose homeostasis [34].

Vasodilatory beta-blockers, such as nebivolol and carvedilol, not only display a better hemodynamic profile but also exert neutral or beneficial effects on glucose metabolism; they are thus associated with a lower incidence of new-onset diabetes, lower morbidity, and lower cardiovascular risk [33, 35–37]. A randomized double-blind study including 72 non-diabetic hypertensive patients reported a significant reduction in insulin sensitivity, a decrease in HDL, and an increase in triglyceride levels after metoprolol treatment, whereas insulin sensitivity increased after carvedilol treatment [38]. There was also a decrease in HDL and an increase in triglyceride levels in patients in the metoprolol-treated group, whereas these parameters remained unchanged in patients in the carvedilol-treated group. In the GEMINI (Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) trial, a randomized, double-blind trial that enrolled 1235 patients with documented type 2 diabetes and hypertension, already receiving ACE-i or an ARB, carvedilol showed a clear metabolic benefit compared to metoprolol [35]. More specifically, carvedilol showed a decrease of 9.1% ($p = 0.004$) in insulin resistance compared with baseline values, whereas no significant difference was seen in the group of patients treated with metoprolol. Additionally, an increase in glycosylated hemoglobin of 0.15% from baseline was seen in the metoprolol group ($p < 0.001$), whereas there was no significant change in the carvedilol group. Although only a few studies have investigated the question, bisoprolol, a beta-1-selective beta-blocker, also appeared to possess a satisfactory hypotensive effect without any adverse effects on glucose metabolism during long-term use [39].

Obesity as a Risk Factor for Hypertension

Obesity is considered a major risk factor for the development of hypertension [40]. It leads to elevated BP and an early onset of cardiovascular morbidity [41]. The relationship between obesity and hypertension has been well established by various cross-sectional studies [42]. Obese individuals have a 3.5-fold greater likelihood of developing hypertension compared to their normal-weight counterparts. Obese individuals with central body fat distribution tend to have higher BP values more than those with peripheral fat distribution [43, 44]. While obese individuals are prone to hypertension, hypertensive patients are also prone to weight gain, especially upper body adiposity [45]. For systolic BP, this is translated into an increase of 4 mmHg for each 4.5 kg of increased weight [46]. According to the Framingham study, the future risk of weight gain is significantly higher in hypertensive patients than in their normotensive counterparts, suggesting that hypertensives are at a high risk for developing obesity [45]. In addition, hypertensive patients have significantly compromised glucose metabolism, lipid metabolism, and insulin sensitivity [40].

The underlying mechanisms for hypertension in obese individuals are multifactorial and complex. Obesity can be characterized by a state of hyperinsulinemia and decreased sensitivity to the metabolic actions of insulin [40]. Hyperinsulinemia leads to a significant increase in BP and the development of hypertension, as described above. Activation of the SNS and the renin–angiotensin system, physical compression of both kidneys, impairment of pressure natriuresis, endothelial dysfunction, and hormonal activity of leptin, neuropeptides, and corticosteroids may also lead to hypertension in obese individuals [40].

Effect of B-Blockers on Obesity and Lipid Metabolism

Dyslipidemia in obesity is characterized by increased triglycerides and free fatty acids, decreased HDL with HDL dysfunction, and normal or slightly increased low-density lipoprotein cholesterol (LDL) levels with increased small dense LDL. Various antihypertensive drugs, such as thiazide diuretics and conventional beta-blockers, were found to have adverse effects on blood lipids [46]. Thiazide diuretics have been used for the treatment of hypertension for a long time. This treatment initially reduces the extracellular fluid volume, plasma volume, and cardiac output [47]. Thiazide diuretics adversely affect lipid metabolism by elevating triglycerides, very-low-density lipoprotein cholesterol (VLDL), total cholesterol, and LDL [48, 49]. However, they exert little or no effect on HDL.

Although conventional beta-blockers have been used in the treatment of hypertension for more than 40 years, their use in the treatment of overweight and obese hypertensives is a matter of debate. They exert adverse effects on weight, heart rate, and lipid and glucose metabolism, which may impair glucose tolerance, increase triglycerides and VLDL, and reduce HDL [50]. They also slow down heart rate, which hampers the patients' exercise potential and puts them at risk of weight gain and obesity. The use of conventional beta-blockers has raised concerns about adverse metabolic effects, and they may have a negative impact on total energy expenditure, which leads to weight gain [34].

New-generation beta-blockers with vasodilatory properties, including carvedilol and nebivolol, have shown a neutral or favorable effect on metabolic profile. In a subanalysis of GEMINI, metoprolol tartrate was associated with increased weight gain compared to carvedilol; weight gain was most pronounced in subjects with hypertension and diabetes who were not taking insulin therapy [51].

In addition, in patients with type 2 diabetes who were taking a renin–angiotensin blocker, the addition of carvedilol for blood pressure control resulted in a significant decrease in triglycerides, total cholesterol, and non-HDL cholesterol levels compared to metoprolol. The use of metoprolol resulted in a significantly greater rate of initiation of statin therapy or an increase in the dose of existing statin therapy when compared with carvedilol use [52].

In a study of 72 nondiabetic patients, metoprolol decreased HDL and increased triglyceride levels; however, no change was observed in either parameter in patients treated with carvedilol [37]. Another randomized clinical trial that included 250 hypertensive patients with baseline dyslipidemia showed that carvedilol increased HDL levels by 11% and decreased triglyceride levels by 13% [53]. However, carvedilol therapy resulted in a reduced quality of life, inhibition of platelet aggregation, and cell proliferation as compared to nebivolol [54, 55].

Potential Mechanisms of Nebivolol Metabolic Effects

The antihypertensive action of nebivolol is achieved via mechanisms that favor the metabolism and have an antidiabetic effect. First, since nebivolol is a highly selective beta-1 adrenergic receptor antagonist, it does not cause the impairment of beta-2-mediated insulin release seen with traditional b-blockers that may decrease the first phase of insulin secretion [56•]. On the other hand, nebivolol acts by increasing NO bioavailability, which might offer a broader favorable metabolic profile. NO bioavailability and signaling has emerged as a central modulator of energy metabolism and a potential mediator of metabolic dysfunction in adipose tissue and obesity [57]. This property may be especially beneficial in an NO-deficient population, such as obese hypertensives and other high-risk populations.

In addition, the effect of nebivolol on insulin resistance can be partially attributed to its ability to significantly improve endothelial dysfunction. This improvement may lead to a reduction in insulin resistance and vice versa [58]. Furthermore, nebivolol is an agonist of endothelial beta-3 adrenoreceptors, which also play a key role in glucose homeostasis and lipid metabolism.

Some of the vasodilatory effects of nebivolol are mediated by an agonist effect on beta-3 adrenergic receptors, inducing sustained NO production through increases in cytosolic calcium concentrations and dephosphorylation of Thr495-eNOS [59]. Beta-3 adrenergic receptors have been mostly thought of as receptors mediating metabolic effects in adipocytes. Selective beta-3 receptor activation exerts potent antidiabetic effects [60].

Experimental data have shown that nebivolol dilates human coronary resistance microarteries via an agonist effect on endothelial beta-3 adrenoreceptors leading to the release of NO [59]. In previous studies, a beta-3 adrenoreceptor agonist was observed to increase lipolysis, fat oxidation, and insulin action in humans [61].

As a consequence of all the above, nebivolol, in contrast to conventional beta-blockers such as metoprolol, improves oxidative stress, decreases plasma-soluble P-selectin, and increases adiponectin levels in hypertensive patients [9••]. Moreover, it attenuates acute inflammatory response as a result of exercise in obese, hypertensive African Americans; increases levels of serum adiponectin by 28%; and decreases leptin levels by 32% [62]. Its effects on oxidative stress and adipokines further contribute to its advantageous metabolic profile.

Effect of Nebivolol Therapy on Insulin Sensitivity and Glucose Metabolism

The effects of nebivolol treatment on insulin sensitivity and glucose metabolism in hypertensive, hypertensive obese, and hypertensive diabetic patients have been evaluated in numerous randomized clinical trials. Marazzi et al. reported an improvement in glucose metabolism (26% reduction in Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]) after 1 month of nebivolol therapy in 233 patients with grade I–II hypertension [56•]. In the YESTONO prospective, postmarketing surveillance study ($n = 2838$), nebivolol significantly reduced BP and improved fasting glucose and glycosylated hemoglobin (HbA1c) in hypertensive diabetic patients over a minimum period of 3 months [63]. In another postmarketing study that included 510 hypertensive diabetic patients, 4 months of nebivolol therapy resulted in a significant reduction in BP and a significant improvement in blood glucose levels (−0.6 mmol/L; $p = 0.021$) [64•]. There is one study comparing the effect of nebivolol and atenolol on BP and metabolic parameters that found no significant difference between them [5]. In contrast to most studies, neither nebivolol nor atenolol adversely affected carbohydrate metabolism in terms of insulin sensitivity, whole body glucose utilization, and HbA1c.

Other data from diabetic patients, comparing nebivolol with ACE-i—which are regarded as first-line therapy in those patients and are known to have a positive effect on glucose metabolism and insulin sensitivity—found no inferiority with regard to metabolic profile and insulin sensitivity [65].

The neutral or beneficial effects of nebivolol are well protected even when it is used in combination with other drugs. In a pilot study of 30 hypertensive hyperlipidemic patients, nebivolol (5 mg daily) in combination with pravastatin (40 mg daily) was found to reduce insulin levels by 10% while maintaining glucose levels [8]. A pooled study of 5 noninterventional studies, including 262 patients with hypertension, revealed that a combination of nebivolol and hydrochlorothiazide effectively controlled hypertension without

affecting glucose levels [66]. A similar effect was also found in the analysis of a diabetic subgroup. Deedwania et al. reported "little or no effect" of add-on nebivolol therapy (in combination with ACE-i or ARB) on glucose metabolism in hypertensive patients with prediabetes [67•].

The new-generation beta-blockers, carvedilol and nebivolol, efficiently and similarly decrease blood pressure. They also have similar favorable effects on glucose, insulin resistance, and lipid profile [68••].

Unlike conventional beta-blockers, nebivolol decreases BP without increasing the risk of incident diabetes [54]. Randomized controlled trials have compared the effect of nebivolol on insulin sensitivity and glucose metabolism with those of other beta-blockers. In a randomized, double-blind study that enrolled 46 patients with metabolic syndrome, metoprolol significantly reduced insulin sensitivity index as compared to nebivolol [69••]. Another double-blind, crossover study compared the metabolic effects of nebivolol and atenolol in 25 hypertensive patients with impaired glucose tolerance [7]. Both nebivolol and atenolol reduced systolic and diastolic BP to the same extent. However, atenolol caused a 20% reduction in insulin sensitivity, whereas nebivolol showed no significant effect.

Effect of Nebivolol Therapy on Obesity and Lipid Metabolism

Nebivolol has a better metabolic profile in hypertensive patients compared to other beta-blockers (Table 2). A previous observation study showed that 6 months' treatment with nebivolol had a favorable effect on HDL but a neutral effect on LDL and triglycerides [10].

Numerous randomized clinical trials have also evaluated the effect of nebivolol on lipid metabolism. A double-blind, parallel-group study, which enrolled 51 patients with mild to moderate hypertension who were treated with nebivolol, showed a significant reduction in total cholesterol (5%) and LDL (8%) levels [71]. Another study, including 233 patients, concluded that nebivolol, either alone or in combination with hydrochlorothiazide, did not alter the lipid profile in naive patients, even after 6 months of treatment [56•]. In a randomized, double-blind study by Pesant et al., no deleterious effect of nebivolol was observed on lipid and glucose metabolism in normometabolic patients with mild to moderate hypertension ($n = 37$) [6]. In a cohort of 18 physically active patients with moderate essential hypertension, the lipid profile remained unchanged after nebivolol treatment, except for a small decrease in HDL [72]. In hypertensive hyperlipidemic patients ($n = 30$), nebivolol and pravastatin combination showed more favorable effects on lipid profile as compared to the combination of atenolol and pravastatin [8].

In 2010, Van Bortel evaluated the effect of nebivolol treatment on lipid profile in a postmarketing study that included 510 hypertensive diabetic patients [64•]. A significant reduction in total cholesterol (−1.45 mmol/L; $p = 0.006$), LDL (−1.32 mmol/L; $p = 0.003$), and LDL/HDL cholesterol ratio (−0.77; $p = 0.011$) was reported after 2 months of treatment. No significant change was found in HDL or triglycerides. Another pooled analysis of 3 placebo-controlled, double-blind multicenter studies, with a total of 2016 patients, showed that nebivolol was well tolerated in moderately obese patients, with neutral effects on carbohydrate and lipid profile [50].

Apart from its neutral or beneficial effects on dyslipidemia, nebivolol offers several other advantages over other antihypertensive drugs that are beneficial for patients with obesity. Obese individuals have an increased risk of cardiovascular disease. Nebivolol displays a significant cardioprotective effect against arrhythmias, left ventricular hypertrophy, congestive heart failure, and sudden cardiac death [73]. It effectively lowers BP by reducing peripheral vascular resistance and increasing stroke volume, while it has no significant effect on cardiac output [74]. Nebivolol also significantly reduces arterial stiffness, which is frequently observed in obese individuals [75]. Oxidative stress has been linked to increased oxidation of lipids mediated by reactive oxygen species [76]. Nebivolol displays strong antioxidative properties via the NO pathway. Thus, nebivolol may also be helpful in inhibiting oxidative damage to lipids. Obese patients have increased SNS activity, resulting in increased cardiac output and hypercirculation [77]. Nebivolol antagonizes enhanced SNS activity and lowers BP. Hence, nebivolol may also help in the management of obesity-related cardiovascular conditions, arterial stiffness, and oxidative stress. An optimal antihypertensive drug used in the treatment of obese hypertensive patient should effectively lower BP, be well tolerated, exert no adverse effects on metabolism, and reduce morbidity and mortality [78]. Nebivolol offers many of these benefits. Hence, it represents a preferred therapeutic choice for the treatment of hypertension in the obese population.

In addition, there are clinical observations that nebivolol, apart from its positive metabolic effects, might have a favorable influence on weight loss in hypertensive diabetic patients, attributable to its beta-3 adrenoceptor activity [70••, 79].

Nebivolol and Antihypertensive Treatment Adherence

Adverse events are one of the major causes of noncompliance among hypertensive patients receiving long-term treatment [80]. Antihypertensive treatment, especially with beta-blockers, suffers from a high rate of discontinuation and nonpersistence. New-generation beta-blockers like nebivolol are associated with a significant improvement in treatment

Table 2 Summary of clinical trials assessing the metabolic effects of nebivolol

Study	Patient population	Design and intervention	Treatment phase	Outcome
Fogari et al. [5]	30 hypertensive patients with diabetes type 2	Randomized, blinded Nebivolol 5 mg vs. atenolol 50 mg	4 weeks	No significant changes in cholesterol (total cholesterol, HDL, LDL), triglycerides plasma levels, HbA1c, and insulin sensitivity
Pesant et al. [6]	Normometabolic subjects with mild to moderate essential hypertension	Randomized, double-blind Nebivolol 5 mg vs. atenolol 50 mg	12 weeks	No significant changes in total cholesterol, HDL (2)-C, HDL (3)-C, LDL-C, VLDL, total triglycerides, total apoB, Lp(a), apoA-I, apoC-III; no significant difference in plasma glucose, insulin, and C-peptide
Rizos et al. [8]	30 hypertensive hyperlipidemic patients	Randomized Nebivolol 5 mg plus pravastatin 40 mg vs. atenolol 50 mg plus pravastatin 40 mg	24 weeks	Atenolol significantly increased triglyceride levels by 19% ($p = 0.05$), nebivolol showed a trend to increase HDL by 8% (NS) and to decrease triglyceride levels by 5% (NS). Atenolol significantly increased Lp(a) by 30% ($p = 0.028$). Nebivolol did not change glucose levels, while insulin levels were reduced by 10% and HOMA was reduced by 20% ($p = 0.05$)
Celik et al. [9••]	80 newly diagnosed hypertensive patients in grade 1 hypertension	Randomized, blinded Nebivolol 5 mg vs. metoprolol 100 mg	6 months	Nebivolol, but not metoprolol, significantly lowered oxidative stress ($p = 0.03$), insulin resistance index ($p = 0.003$), and plasma sP-selectin levels ($p = 0.008$) and increased adiponectin levels ($p = 0.04$)
Peter et al. [10]	26 patients with mild to moderate hypertension	Observational study Nebivolol 5 mg	6 months	No significant changes in serum cholesterol and triglycerides but a significant increase in HDL cholesterol ($p = 0.009$)
Van Bortel [64•]	510 patients with hypertension and diabetes mellitus	Observational study Nebivolol in clinical practice	4 months	A significant improvement in blood glucose ($p = 0.021$). Significant reductions in total cholesterol ($p = 0.006$), LDL ($p = 0.003$), and LDL/HDL cholesterol ratio ($p = 0.011$). No significant changes were seen in HDL cholesterol or triglycerides
Kaiser et al. [65]	12 hypertensive patients with diabetes type 2	Randomized, double-blind crossover trial Nebivolol 5 mg vs. enalapril 10 mg	12 weeks	No significant differences in insulin sensitivity
Deedwania et al. [67•]	537 hypertensive patients with prediabetes	Randomized, double-blind, placebo and active-controlled patients were randomized (2:2:1) to add-on treatment with nebivolol (5 mg/day), HCTZ (12.5 mg/day), or placebo, titrated to 10, 20, or 40 mg/day nebivolol, or 25 mg/day (HCTZ)	12 weeks	The mean changes in the area under the curve for oral glucose tolerance test were 0.0 mg/dL (nebivolol), 6.9 mg/dL (HCTZ; $p = 0.024$ vs. nebivolol), and 1.0 mg/dL (placebo). In the placebo group, 6 of 100 (6.0%) participants were diagnosed with diabetes during the study, compared with 24 of 217 (11.1%) in the nebivolol group and 33 of 209 (15.8%) in the HCTZ group ($p = $ NS)
Ozyıldız et al. [68••]	80 hypertensive patients	Randomized, open-label Nebivolol 5 mg vs. carvedilol 25 mg	4 months	Serum glucose ($p < 0.001$), insulin ($p < 0.01$), HOMA-IR ($p < 0.01$), HDL ($p < 0.001$), LDL ($p < 0.001$), total cholesterol ($p < 0.001$), and apolipoprotein B ($p < 0.05$) levels decreased in a similar manner in the carvedilol and nebivolol groups after treatment compared to those before treatment
Ayers et al. [69••]	46 patients with metabolic syndrome	Randomized, double-blind, crossover trial Nebivolol 5 mg vs. metoprolol succinate ER 100 mg	12 weeks	Metoprolol significantly decreased the insulin sensitivity index. In contrast, nebivolol did not affect insulin sensitivity ($p = 0.003$)
Ladage et al. [70••]	5031 with mild to moderate hypertension and diabetes type 2	Observational study Nebivolol 5 mg	12 weeks	Body weight and BMI were reduced in patients. The amount of weight reduction was significantly higher in male patients (-1.1 ± 0.06 kg) than in female patients (-0.71 ± 0.06 kg; $p < 0.05$). This finding was also reflected in the BMI (-0.26 ± 0.02 vs. -0.35 ± 0.02; $p < 0.05$)

apoB apolipoprotein B, *apoA-I* apolipoprotein A-I, *apoC-III* apolipoprotein C-III, *BMI* body mass index, *HbA1c* hemoglobin A1c, *HCTZ* hydrochlorothiazide, *HOMA-IR* Homeostasis Model Assessment of Insulin Resistance, *Lp(a)* lipoprotein (a)

persistence. This is mainly due to their good safety profile and low rate of adverse effects. The discontinuation rate due to adverse events among nebivolol-treated patients (all dosages) was low (2.6%) and comparable to that observed with placebo (2.0%) [81]. In a randomized double-blind study, Bhosale et al. reported that nebivolol was better tolerated than atenolol, as it showed a lower incidence of adverse effects (36.84% with atenolol vs. 12.82% with nebivolol) [82•]. Nebivolol showed comparable tolerability to placebo in both obese and nonobese African American patients, a population that is difficult to treat [83].

A significant number of hypertensive patients with diabetes mellitus (86.5%) reported their experience with nebivolol treatment as good to very good, along with a lower incidence of adverse effects (3%) after 17 weeks [64•]. A lower incidence of adverse effects and a higher satisfaction rate with nebivolol treatment may significantly improve patient compliance, as it may encourage patients to adhere to the treatment in the long term. Because of their adverse effects on metabolism, many antihypertensive drugs, such as conventional beta-blockers, may not be the preferred agents for the management of BP.

Conclusions

Nebivolol is a well-tolerated cardioselective beta-blocker that significantly reduces BP and may have advantages in high-risk populations, such as diabetics, obese patients, and patients with metabolic syndrome. Nebivolol, with its additional antioxidative properties, displays neutral or beneficial effects on insulin sensitivity and lipid metabolism in hypertensive patients. BP can be controlled effectively by incorporating lifestyle modifications and new-generation beta-blockers like nebivolol as therapeutic strategies for the comprehensive management of hypertension. It is important to dissociate newer from conventional b-blockers, since the newer drugs offer the advantages of better patient compliance and relatively safe metabolic effects on insulin sensitivity and lipid metabolism in hypertensive patients.

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Compliance with Ethical Standards

Conflict of Interest Drs. Marketou, Gupta, and Vardas declare no conflicts of interest relevant to this manuscript. Dr. Jain reports grants from A. Manarini, Singapore, and support from SPRIM Asia Pacific Ltd, Singapore.

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that the addition of hydrochlorothiazide on nebivolol treatment optimizes blood pressure control in a high number of patients resistant to monotherapy without a negative impact on patients' glucose and lipid profile.

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